

### Search Strategy

FILE 'MEDLINE, USPATFULL, WPIDS' ENTERED AT 19:30:28 ON 29 JUL 1997  
E DOUGLAS T/AU

L1 17 FILE MEDLINE  
L2 0 FILE USPATFULL  
L3 1 FILE WPIDS

TOTAL FOR ALL FILES

L4 18 S E3  
E YOUNG M J/AU  
L5 105 FILE MEDLINE  
L6 0 FILE USPATFULL  
L7 10 FILE WPIDS

TOTAL FOR ALL FILES

L8 115 S E3  
L9 0 FILE MEDLINE  
L10 0 FILE USPATFULL  
L11 0 FILE WPIDS

TOTAL FOR ALL FILES

L12 0 S L5 AND (NANOPARTICLE OR NANOSCALE OR NANOCOMPOSITE)  
L13 87 FILE MEDLINE  
L14 185 FILE USPATFULL  
L15 57 FILE WPIDS

TOTAL FOR ALL FILES

L16 329 S (NANOPARTICLE OR NANOCOMPOSITE OR NANOSCALE)  
L17 0 FILE MEDLINE  
L18 0 FILE USPATFULL  
L19 0 FILE WPIDS

TOTAL FOR ALL FILES

L20 0 S L16 AND (CCMV OR COWPEA CHLOROTIC MOTTLE VIRUS)  
L21 0 FILE MEDLINE  
L22 29 FILE USPATFULL  
L23 0 FILE WPIDS

TOTAL FOR ALL FILES

L24 29 S L16 AND (NANOPARTICLE/AB OR NANOCOMPOSITE/AB OR NANOSCA  
L25 82 FILE MEDLINE  
L26 7 FILE USPATFULL  
L27 0 FILE WPIDS

TOTAL FOR ALL FILES

L28 89 S (CCMV OR COWPEA CHLOROTIC MOTTLE VIRUS)  
L29 27 FILE MEDLINE  
L30 6 FILE USPATFULL  
L31 0 FILE WPIDS

TOTAL FOR ALL FILES

L32 33 S L28 AND (COAT PROTEIN)  
L33 6 FILE MEDLINE  
L34 6 FILE USPATFULL  
L35 0 FILE WPIDS

TOTAL FOR ALL FILES

L36 12 S L32 AND PARTICLE?  
L37 311 FILE MEDLINE  
L38 56 FILE USPATFULL

L39 5 FILE WPIDS  
TOTAL FOR ALL FILES  
L40 372 S VIRAL ASSEMBLY OR VIRION ASSEMBLY  
L41 3 FILE MEDLINE  
L42 18 FILE USPATFULL  
L43 0 FILE WPIDS  
TOTAL FOR ALL FILES  
L44 21 S L40 AND REVIEW?

L13 ANSWER 47 OF 87 MEDLINE

94349589 Nanotechnology: basic concepts and definitions. Kaehler T.  
(Apple Computer, Cupertino, CA 95014.. )CLINICAL CHEMISTRY, (1994  
Sep) 40 (9) 1797-9. Journal code: DBZ. ISSN: 0009-9147. Pub.  
country: United States. Language: English.

AB Molecular nanotechnology is an engineering discipline in which the  
goal is to build devices and structures that have every atom in the  
proper place. By means of this general purpose material-processing  
technology it will be possible to build almost any rigid, covalently  
bonded structure. Identical parts will be truly identical, enabling  
energy conversion and computation systems to have extremely high  
performance and reliability. Assembly will be done by  
mechanosynthesis, the process of holding two reactive molecules in  
contact with each other in a controlled orientation. Synthesis will  
be done on \*\*\*nanoscale\*\*\* assembly lines called molecular  
mills, where systems of moving belts will press individual molecules  
together and catalyze 10(6) reactions/s per station.  
High-performance mechanical computers will use moving rods to block  
the motion of other rods. The most important physical limit will be  
radiation damage. Without redundancy, a subsystem lasting 100 years  
will be limited to 10(6) nm3.

L13 ANSWER 1 OF 87 MEDLINE

97321119 Peptomer aluminum oxide \*\*\*nanoparticle\*\*\* conjugates as  
systemic and mucosal vaccine candidates: synthesis and  
characterization of a conjugate derived from the C4 domain of  
HIV-1MN gp120. Frey A; Neutra M R; Robey F A. (Department of  
Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.  
)BIOCONJUGATE CHEMISTRY, (1997 May-Jun) 8 (3) 424-33. Journal code:  
ALT. ISSN: 1043-1802. Pub. country: United States. Language:  
English.

AB Peptomers are polymers composed of peptides that are specifically  
cross-linked in a head-to-tail fashion. Recently, a peptomer  
composed of an amphipathic peptide from the C4 domain of HIV-1MN  
gp120 was shown to display a prominent alpha-helical conformation  
that, as an immunogen, elicited rabbit antibodies recognizing native  
and recombinant gp120 [Robey et al. (1995) J. Biol. Chem. 270,  
23918-23921]. For the present study, we synthesized a conjugate  
composed of the C4 peptomer covalently linked to calcinated aluminum  
oxide nanoparticles. The nanoparticles were first reacted with  
(3-aminopropyl)-triethoxysilane to provide an amine load of 15.9  
mmol of R-NH2/g of solid. The amine-modified aluminum oxide  
nanoparticles then were reacted with N-acetylhomocysteine  
thiolactone at pH 10 to place a reactive thiol on the nanoparticles.  
A bromoacetylated C4 peptomer, modified at the epsilon-amines of  
lysine residues, then was reacted with the thiolated nanoparticles  
to give the peptomer covalently linked to aluminum oxide via a  
thioether bond. The peptomer load was determined to be 16 mg of  
peptomer/g of particles, a 55% theoretical yield. Particle shape and  
size of the peptomer-conjugated alumina were analyzed by electron  
microscopy and displayed a mean maximum diameter of 355 nm and a  
mean minimum diameter of 113 nm, well within the desired size range  
of 300 nm believed to be optimal for mucosal immunization purposes.  
Experimentally determined values of mean particle diameters,  
specific surface area, and specific peptomer load provided the

information necessary to calculate the mean antigen load, which was determined to be 53000 +/- 42000 peptomer epitopes per particle. Peptomer-alumina conjugates, such as that described here, could form the basis of a new class of biomaterial that combines a chemically defined organic immunogen with a nontoxic chemically defined inorganic adjuvant.

L13 ANSWER 3 OF 87 MEDLINE

97225923 Nucleoprotein-based \*\*\*nanoscale\*\*\* assembly. Smith S S; Niu L; Baker D J; Wendel J A; Kane S E; Joy D S. (Department of Cell and Tumor Biology, City of Hope National Medical Center, Duarte, CA 91010, USA. )PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Mar 18) 94 (6) 2162-7. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB A system for addressing in the construction of macromolecular assemblies can be based on the biospecificity of DNA (cytosine-5) methyltransferases and the capacity of these enzymes to form abortive covalent complexes at targeted 5-fluorocytosine residues in DNA. Using this system, macromolecular assemblies have been created using two representative methyltransferases: M-HhaI and M x MspI. When 5-fluorocytosine (F) is placed at the targeted cytosine in each recognition sequence in a synthetic oligodeoxynucleotide (GFGC for M x HhaI or FCGG for M x MspI), we show that the first recognition sequence becomes an address for M x HhaI, while the second sequence becomes an address for M x MspI. A chimeric enzyme containing a dodecapeptide antigen linked to the C terminus of M-HhaI retained its recognition specificity. That specificity served to address the linked peptide to the GFGC recognition site in DNA. With this assembly system components can be placed in a preselected order on the DNA helix. Axial spacing for adjacent addresses can be guided by the observed kinetic footprint of each methyltransferase. Axial rotation of the addressable protein can be guided by the screw axis of the DNA helix. The system has significant potential in the general construction of macromolecular assemblies. We anticipate that these assemblies will be useful in the construction of regular protein arrays for structural analysis, in the construction of protein-DNA systems as models of chromatin and the synaptonemal complex, and in the construction of macromolecular devices.

L13 ANSWER 6 OF 87 MEDLINE

97157614 Nanotechnology for biomaterials engineering: structural characterization of amphiphilic polymeric nanoparticles by 1H NMR spectroscopy. Hrkach J S; Peracchia M T; Domb A; Lotan N; Langer R. (Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 02139, USA. )BIOMATERIALS, (1997 Jan) 18 (1) 27-30. Journal code: A4P. ISSN: 0142-9612. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Nanoparticles composed of diblock poly(D,L-lactide-co-glycolide)-poly(ethylene glycol) (PLGA-PEG) or a branched, multiblock PLA-(PEG)3 were prepared by the single emulsion technique. Results of previous studies of these nanoparticles suggested that their structure is of the core-corona type with a polyester core and an outer PEG coating. In the present study, 1H NMR spectroscopy was utilized to provide direct evidence of the structure of these nanoparticles suspended in an aqueous environment. The results confirm the existence of the core-corona structure under these conditions, and show that the PEG moieties extend out from the \*\*\*nanoparticle\*\*\* core into the aqueous environment, and exhibit chain mobility similar to that of PEG in solution.

L13 ANSWER 7 OF 87 MEDLINE

97149393 Body distribution of free, liposomal and \*\*\*nanoparticle\*\*\* -associated mitoxantrone in B16-melanoma-bearing mice. Reszka R; Beck P; Fichtner I; Hentschel M; Richter J; Kreuter J. (Max-Delbruck Center for Molecular Medicine, Berlin, Germany. )JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Jan) 280 (1) 232-7. Journal code: JP3. ISSN: 0022-3565. Pub. country: United

States. Language: English.

AB B16-melanoma-bearing mice were treated with four different formulations containing equivalent doses of the highly effective antineoplastic drug mitoxantrone. The formulations were: A mitoxantrone solution, a negatively charged liposome preparation (small unilamellar vesicles), a <sup>14</sup>C-labeled polybutylcyanoacrylate-(PBCA) \*\*\*nanoparticle\*\*\* suspension, and a suspension of poloxamine 1508-coated <sup>14</sup>C-PBCA-nanoparticles. After 1, 4 and 24 hr, three animals of each group were killed and the mitoxantrone concentrations in the blood, tumor, liver, spleen, heart and bone marrow were determined using an high performance liquid chromatography technique. Additionally, the concentrations of PBCA particles in the same tissues were measured by scintillation counting to compare the mitoxantrone distribution with the corresponding PBCA \*\*\*nanoparticle\*\*\* distribution. Each formulation led to a different body distribution profile of the drug. Liposomes drastically increased the blood level of mitoxantrone even after 24 hr, although free drug was cleared quickly. Liposomes also raised the concentration in the liver and spleen, but not the drug level in the tumor. PBCA-nanoparticles considerably increased the mitoxantrone concentrations in tumor, heart and spleen. However, the increase in tumor concentrations was not statistically significant due to the high variability. Nevertheless, the tumor growth was reduced significantly ( $P < .05$ ) compared to both, the liposome and the solution preparation. The \*\*\*nanoparticle\*\*\* polymer concentrations did not completely mirror those of the drug concentrations. Especially in the heart, where no \*\*\*nanoparticle\*\*\* polymer radioactivity was found, the particle concentration did not completely correspond to the mitoxantrone concentration, revealing that a part of the drug was lost from the particles. These pharmacokinetic results correspond to parallel therapeutic effects obtained with mitoxantrone-loaded nanoparticles and liposomes in the B16 melanoma.

L13 ANSWER 8 OF 87 MEDLINE

97140610 Gastrointestinal uptake of biodegradable microparticles: effect of particle size. Desai M P; Labhasetwar V; Amidon G L; Levy R J. (University of Michigan, Division of Pediatric Cardiology, Ann Arbor 48109, USA. ) PHARMACEUTICAL RESEARCH, (1996 Dec) 13 (12) 1838-45. Journal code: PHS. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB PURPOSE: To investigate the effect of microparticle size on gastrointestinal tissue uptake. METHODS: Biodegradable microparticles of various sizes using polylactic polyglycolic acid (50:50) co-polymer (100 nm, 500 nm, 1 micron, and 10 microns) and bovine serum albumin as a model protein were formulated by water-in-oil-in-water emulsion solvent evaporation technique. The uptake of microparticles was studied in rat in situ intestinal loop model and quantitatively analyzed for efficiency of uptake. RESULTS: In general, the efficiency of uptake of 100 nm size particles by the intestinal tissue was 15-250 fold higher compared to larger size microparticles. The efficiency of uptake was dependent on the type of tissue, such as Peyer's patch and non patch as well as on the location of the tissue collected i.e. duodenum or ileum. Depending on the size of microparticles, the Peyer's patch tissue had 2-200 fold higher uptake of particles than the non-patch tissue collected from the same region of the intestine. Histological evaluation of the tissue sections demonstrated that 100 nm particles were diffused throughout the submucosal layers while the larger size nano/microparticles were predominantly localized in the epithelial lining of the tissue. CONCLUSIONS: There is a microparticle size dependent exclusion phenomena in the gastrointestinal mucosal tissue with 100 nm size particles showing significantly greater tissue uptake. This has important implications in designing of \*\*\*nanoparticle\*\*\* -based oral drug delivery systems, such as an oral vaccine system.

L13 ANSWER 9 OF 87 MEDLINE

97118365 Macrophage targeting of azidothymidine: a promising strategy for AIDS therapy. Losenberg R; Kreuter J. (Institut für Pharmazeutische Technologie, Johann Wolfgang Goethe-Universität, Frankfurt, Germany. )AIDS RESEARCH AND HUMAN RETROVIRUSES, (1996 Dec 10) 12 (18) 1709-15. Journal code: ART. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Macrophages play an important role in the immunopathogenesis of AIDS. The objective of this study was to investigate the possibility of specific targeting of antivirals such as azidothymidine (AZT) to macrophages, using nanoparticles as a colloidal drug carrier. The body distribution of AZT bound to nanoparticles and as a control solution was studied in rats after intravenous and peroral administration. <sup>14</sup>C-Labeled AZT was bound to nanoparticles in the presence of bis(2-ethylhexyl)sulfosuccinate sodium. The radioactivity was measured in different organs including those containing large numbers of macrophages. After intravenous injection, the concentrations of AZT were up to 18 times higher in organs belonging to the reticuloendothelial system (RES) when the drug was bound to nanoparticles than after injection of an aqueous AZT solution. Likewise, after oral administration the

\*\*\*nanoparticle\*\*\* formulation delivered AZT more efficiently to the RES than the aqueous solution. In addition, the blood concentration was significantly higher after oral administration of nanoparticles. These results demonstrate that nanoparticles are a promising drug-targeting system for AZT to the RES organs. The increase in drug availability at the sites containing abundant macrophages may allow a reduction in dosage to avoid systemic

L13 ANSWER 12 OF 87 MEDLINE

97031978 Cells involved in the capture of nanoparticles in hematopoietic organs. Gibaud S; Demoy M; Andreux J P; Weingarten C; Gouritin B; Couvreur P. (Laboratoire de Physico-Chimie, Pharmacotechnie et Biopharmacie, URA-CNRS 1218, Faculté de Pharmacie, Université Paris XI, Chatenay-Malabry, France. )JOURNAL OF PHARMACEUTICAL SCIENCES, (1996 Sep) 85 (9) 944-50. Journal code: JO7. ISSN: 0022-3549. Pub. country: United States. Language: English.

AB The affinity of nanoparticles for hematopoietic organs could be valuable for the targeting of certain stimulating factors to those tissues, but this affinity should also be taken into account in the toxicological evaluation of those carriers, especially when they are loaded with antimitotic compounds such as doxorubicin. However, the cells responsible for the capture of the nanoparticles and their localization in these organs is an important point to know before trying to modulate the \*\*\*nanoparticle\*\*\* 's tissue distribution. Thus, we have studied, in this paper, the capture, the localization, and the retention in the bone marrow and in the spleen of biodegradable poly(isohexyl cyanoacrylate) nanoparticles as well as of nonbiodegradable polystyrene nanoparticles. The histological localization of these nanoparticles has been completed by cytological localization with a method used in cytochemistry for the evaluation of intracellular accumulation of various substances, such as iron deposits in bone marrow sideroblasts. These data indicate that, in the bone marrow, after a quick passage through the endothelium, nanoparticles were dispersed throughout in the tissue and captured by all types of phagocytizing cells. In the spleen, nanoparticles were mainly localized in large angular capturing cells in the marginal zone of the lymphoid follicles.

L13 ANSWER 13 OF 87 MEDLINE

97000314 Modelling \*\*\*nanoscale\*\*\* fluid dynamics and transport in physiological flows. Ciofalo M; Collins M W; Hennessy T R. (Department of Mechanical Engineering and Aeronautics, City University, London, UK. )MEDICAL ENGINEERING AND PHYSICS, (1996 Sep) 18 (6) 437-51. Ref: 88. Journal code: BZU. ISSN: 1350-4533. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The concept of nanotechnology is discussed, and its connection with biomedical engineering is elucidated. For the specific field of \*\*\*nanoscale\*\*\* flow and transport problems of physiological

relevance, some typical examples are presented, and their interaction is discussed for some classic biomechanical problems like the flow in arteries with blood-wall coupling. Then, existing computational models are presented and classified according to the length scale of interest, with emphasis on particle-fluid problems. Final remarks address the essential unity of biomedical and engineering behaviour and the possible relevance to small-scale industrial research.

L13 ANSWER 21 OF 87 MEDLINE

96353169 Pharmacokinetics of a novel HIV-1 protease inhibitor incorporated into biodegradable or enteric nanoparticles following intravenous and oral administration to mice. Leroux J C; Cozens R; Roesel J L; Galli B; Kubel F; Doelker E; Gurny R. (School of Pharmacy, University of Geneva, Switzerland. ) JOURNAL OF PHARMACEUTICAL SCIENCES, (1995 Dec) 84 (12) 1387-91. Journal code: JO7. ISSN: 0022-3549. Pub. country: United States. Language: English.

AB CGP 57813 is a peptidomimetic inhibitor of human immunodeficiency virus type 1 (HIV-1) protease. This lipophilic compound was successfully entrapped into poly(D,L-lactic acid) (PLA) and pH sensitive methacrylic acid copolymers \*\*\*nanoparticle\*\*\*. The intravenous administration to mice of PLA nanoparticles loaded with CGP 57813 resulted in a 2-fold increase of the area under the plasma concentration-time curve, compared to a control solution. An increase in the elimination half-life (from 13 to 61 min) and in the apparent volume of distribution (1.7-3.6 L/kg) was observed for the \*\*\*nanoparticle\*\*\* incorporated compound vs control solution. Following oral administration, only nanoparticles made of the methacrylic acid copolymer soluble at low pH provided sufficient plasma levels of CGP 57813. In vitro, these nanoparticles dissolved completely within 5 min at pH 5.8. PLA nanoparticles, which are insoluble in the gastrointestinal tract, did not provide significant plasma concentrations of CGP 57813. From these observations, one can conclude that the passage of intact PLA nanoparticles across the gastrointestinal mucosa appears to be very low.

L13 ANSWER 22 OF 87 MEDLINE

96338368 Efficiency of nanoparticles as a carrier system for antiviral agents in human immunodeficiency virus-infected human monocytes/macrophages in vitro. Bender A R; von Briesen H; Kreuter J; Duncan I B; Rubsamens-Waigmann H. (Chemotherapeutical Research Institute Georg-Speyer-Haus, Frankfurt am Main, Germany. ) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Jun) 40 (6) 1467-71. Journal code: 6HK. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Polyhexylcyanoacrylate nanoparticles loaded with either the human immunodeficiency virus (HIV) protease inhibitor saquinavir (Ro 31-8959) or the nucleoside analog zalcitabine (2',3'-dideoxycytidine) were prepared by emulsion polymerization and tested for antiviral activity in primary human monocytes/macrophages in vitro. Both nanoparticulate formulations led to a dose-dependent reduction of HIV type 1 antigen production. While \*\*\*nanoparticle\*\*\*-bound zalcitabine showed no superiority to an aqueous solution of the drug, a significantly higher efficacy was observed with saquinavir-loaded nanoparticles. In acutely infected cells, an aqueous solution of saquinavir showed little antiviral activity at concentrations below 10 nM, whereas the nanoparticulate formulation exhibited a good antiviral effect at a concentration of 1 nM and a still-significant antigen reduction at 0.1 nM (50% inhibitory concentrations = 4.23 nM for the free drug and 0.39 nM for the \*\*\*nanoparticle\*\*\*-bound drug). At a concentration of 100 nM, saquinavir was completely inactive in chronically HIV-infected macrophages, but when bound to nanoparticles it caused a 35% decrease in antigen production. Using nanoparticles as a drug carrier system could improve the delivery of antiviral agents to the mononuclear phagocyte system in vivo, overcoming pharmacokinetic problems and enhancing the activities of drugs for the treatment of

L13 ANSWER 24 OF 87 MEDLINE

96337983 Biomembrane templates for \*\*\*nanoscale\*\*\* conduits and networks. Evans E; Bowman H; Leung A; Needham D; Tirrell D. (Department of Physics, University of British Columbia, Vancouver, British Columbia, Canada V6T 1W5. )SCIENCE, (1996 Aug 16) 273 (5277) 933-5. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Long nanotubes of fluid-lipid bilayers can be used to create templates for photochemical polymerization into solid-phase conduits and networks. Each nanotube is pulled from a micropipette-held feeder vesicle by mechanical retraction of the vesicle after molecular bonding to a rigid substrate. The caliber of the tube is controlled precisely in a range from 20 to 200 nanometers merely by setting the suction pressure in the micropipette. Branched conduits can be formed by coalescing separate nanotubes drawn serially from the feeder vesicle surface. Single nanotubes and nanotube junctions can be linked together between bonding sites on a surface to create a functionalized network. After assembly, the templates can be stabilized by photoinitiated radical cross-linking of macromonomers contained in the aqueous solution confined by the lipid bilayer

L13 ANSWER 29 OF 87 MEDLINE

96110442 Physicochemical characteristics of gentamicin polybutylcyanoacrylate nanoparticles. Zhang Q; Liao G; Yin H. (Department of Pharmaceutics, School of Pharmacy.. )HUA-HSI I KO TA HSUEH HSUEH PAO [JOURNAL OF WEST CHINA UNIVERSITY OF MEDICAL SCIENCES], (1995 Jun) 26 (2) 172-6. Journal code: GEB. ISSN: 0257-7712. Pub. country: China. Language: Chinese.

AB Several formulations of gentamicin \*\*\*nanoparticle\*\*\* (GM-NP) colloids were prepared by the emulsion polymerization technique using the polybutylcyanoacrylate as the carrier. Various kinds of physicochemical characteristics, such as particle size and size distribution, drug loading and associating ratio, surface zeta potential, surface tension, turbidity, relative density, viscosity, refractive index and acidity were observed, determined and compared. The results of the experiments have contributed to a full understanding of the physicochemical characteristics of gentamicin nanoparticles and also provided a basis for the establishment of the quality evaluation methods.

L13 ANSWER 30 OF 87 MEDLINE

96110440 Adsorption of aclacinomycin A onto polyisobutylcyanoacrylate nanoparticles. Jiang X; Liao G. (Department of Pharmaceutics, School of Pharmacy.. )HUA-HSI I KO TA HSUEH HSUEH PAO [JOURNAL OF WEST CHINA UNIVERSITY OF MEDICAL SCIENCES], (1995 Jun) 26 (2) 163-6. Journal code: GEB. ISSN: 0257-7712. Pub. country: China. Language: Chinese.

AB The mechanism of adsorption of aclacinomycin A onto polyisobutylcyanoacrylate \*\*\*nanoparticle\*\*\* and the factors effecting the adsorption were studied. The adsorption process reached equilibrium in 15 minutes. The results showed that the surface charge densities of the nanoparticles, pH, ionic strength and temperature effected the adsorption. Adsorption isotherms of aclacinomycin A onto polyisobutylcyanoacrylate nanoparticles could be described with Freundlich equation  $Y = 1.0188 C^{0.6494}$  ( $r = 0.9945$ ) and with Langmuir equation  $C/Y = 0.7363C + 0.4027$  ( $r = 0.9331$ ) respectively. The main actions between aclacinomycin A and polyisobutylcyanoacrylate nanoparticles were electrostatic and ionic action.

L13 ANSWER 31 OF 87 MEDLINE

96057697 Nanoparticles as adjuvants for vaccines. Kreuter J. (Institute for Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany.. )PHARMACEUTICAL BIOTECHNOLOGY, (1995) 6 463-72. Ref: 32. Journal code: BYR. ISSN: 1078-0467. Pub. country: United States. Language: English.

AB PMMA \*\*\*nanoparticle\*\*\* adjuvants can be manufactured in a physicochemically reproducible manner. Their particle size can be controlled within narrow limits. Immunogens may be either incorporated or adsorbed to these nanoparticles. PMMA nanoparticles induced significantly higher and more prolonged antibody responses against a variety of immunogens, including influenza virions and subunit vaccines, BSA, and HIV-1 and HIV-2 split vaccines. In addition, a protective immune response against challenge with live influenza virus was induced and a better stability of the immunogen was observed after incorporation or adsorption of influenza virions or subunits to PMMA nanoparticles. The observation that PMMA did not induce antibodies against gp120 contained in the HIV-2 split vaccine demonstrates that different adjuvants or carriers may be required for different antigens. A combination of two or more different adjuvants or carriers may be necessary to induce the optimal immune response against antigen mixtures as present in most vaccine preparations. PMMA seems to be a safe adjuvant material. It is very slowly biodegradable and has been used in surgery in humans for over 40 years, and now warrants continued investigation as a vaccine adjuvant.

L13 ANSWER 37 OF 87 MEDLINE

95256848 Reconstitution of manganese oxide cores in horse spleen and recombinant ferritins. Meldrum F C; Douglas T; Levi S; Arosio P; Mann S. (School of Chemistry, University of Bath, UK. ) JOURNAL OF INORGANIC BIOCHEMISTRY, (1995 Apr) 58 (1) 59-68. Journal code: JAR. ISSN: 0162-0134. Pub. country: United States. Language: English.

AB The formation of Mn(III) oxyhydroxide (MnOOH) cores within the \*\*\*nanoscale\*\*\* cavity of the iron storage protein ferritin has been investigated by electron microscopy and visible absorption spectroscopy. At pH 8.9, discrete amorphous MnOOH cores were formed within horse spleen apoferritin at a range of metal:protein ratios, as well as in ferritin molecules seeded with a small ferrihydrite nucleus. Analysis of the resultant core size distributions showed that the reconstitution of horse spleen apoferritin with Mn(II) was similar to that observed previously for Fe(II) reconstitution in recombinant human L-chain ferritin, suggesting that horse spleen apoferritin does not exhibit Mn(II) oxidase activity at pH 8.9. Reconstitution with MnOOH shows essentially "all-or-nothing" behavior in which many protein molecules remain unmineralized whilst others are loaded to maximum capacity. Kinetic studies showed no significant differences between horse spleen ferritin, recombinant H- and L-chain homopolymers, and H-chain variants containing site-directed modifications at the ferroxidase and putative Fe nucleation centers. Our results indicate that the reconstitution of ferritin with MnOOH cores proceeds by a nonspecific pathway. We propose that the outer surface of the protein inhibits the development of MnOOH nuclei in bulk solution whereas the inner surface is inactive, enabling nucleation and growth to proceed unperturbed within the cavity. One possibility is that differences in the general polyelectrolyte properties of these two surfaces, rather than site-specific charges, account for the "Janus" behavior of the molecule. A similar mechanism might also increase the specificity of iron oxide mineralization in ferritins that lack ferroxidase centers.

L13 ANSWER 40 OF 87 MEDLINE

95158870 Cooperative organization of inorganic-surfactant and biomimetic assemblies. Firouzi A; Kumar D; Bull L M; Besier T; Sieger P; Huo Q; Walker S A; Zasadzinski J A; Glinka C; Nicol J; et al. (Department of Chemical Engineering, University of California, Santa Barbara 93106. ) SCIENCE, (1995 Feb 24) 267 (5201) 1138-43. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB A model that makes use of the cooperative organization of inorganic and organic molecular species into three dimensionally structured arrays is generalized for the synthesis of \*\*\*nanocomposite\*\*\* materials. In this model, the properties and structure of a system



are determined by dynamic interplay among ion-pair inorganic and organic species, so that different phases can be readily obtained through small variations of controllable synthesis parameters, including mixture composition and temperature. Nucleation, growth, and phase transitions may be directed by the charge density, coordination, and steric requirements of the inorganic and organic species at the interface and not necessarily by a preformed structure. A specific example is presented in which organic molecules in the presence of multiply charged silicate oligomers self-assemble into silicatropic liquid crystals. The organization of these silicate-surfactant mesophases is investigated with and without interfacial silicate condensation to separate the effects of self-assembly from the kinetics of silicate polymerization.

L13 ANSWER 57 OF 87 MEDLINE

94067316 Self-assembling organic nanotubes based on a cyclic peptide architecture [published erratum appears in Nature 1994 Dec 15;372(6507):709]. Ghadiri M R; Granja J R; Milligan R A; McRee D E; Khazanovich N. (Department of Chemistry, Scripps Research Institute, La Jolla, California 92037.. )NATURE, (1993 Nov 25) 366 (6453) 324-7. Journal code: NSC. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Hollow tubular structures of molecular dimensions may offer a variety of applications in chemistry, biochemistry and materials science. Concentric carbon nanotubes have attracted a great deal of attention, while the three-dimensional tubular pore structures of molecular sieves have long been exploited industrially.

\*\*\*Nanoscale\*\*\* tubes based on organic materials have also been reported previously. Here we report the design, synthesis and characterization of a new class of organic nanotubes based on rationally designed cyclic polypeptides. When protonated, these compounds crystallize into tubular structures hundreds of nanometres long, with internal diameters of 7-8 Å. Support for the proposed tubular structures is provided by electron microscopy, electron diffraction, Fourier-transform infrared spectroscopy and molecular modelling. These tubes are open-ended, with uniform shape and internal diameter. We anticipate that they may have possible applications in inclusion chemistry, catalysis, molecular electronics and molecular separation technology.

L13 ANSWER 84 OF 87 MEDLINE

87159581 Nanoparticles in drug delivery. Douglas S J; Davis S S; Illum L. CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, (1987) 3 (3) 233-61. Ref: 167. Journal code: CRI. ISSN: 0743-4863. Pub. country: United States. Language: English.

AB Alkylcyanoacrylates can be polymerized in acidified aqueous media by a process of anionic polymerization. The small particles produced tend to be monodisperse and have sizes in the range of 20 to 3000 nm depending upon the polymerization conditions and the presence of additives in the form of surfactants and other stabilizers. The polyalkylcyanoacrylate nanoparticles so produced have been studied in recent years as a possible means of targeting drugs to specific sites in the body, with particular emphasis in cancer chemotherapy. The small colloidal carriers are biodegradable and drug substances can be incorporated normally by a process of surface adsorption. The review by Davis and others considers the formulation of nanoparticles, the important physicochemical variables such as pH, monomer concentration, added stabilizers, ionic strengths, etc., as well as the characteristics of the particle so created in terms of surface charge, particle size, and molecular weight. Monodisperse particles in the range of 20 to 3000 nm can be obtained. In addition, by the use of stabilizers such as dextran and its derivatives, which can be incorporated into the \*\*\*nanoparticle\*\*\* surface by a process of polymer grafting, it is possible to make nanoparticles with interesting surface characteristics and different surface charges (sign). The stability of nanoparticles in vitro and their biodegradation in vivo are examined, and the possible formation of toxic products such as formaldehyde is highlighted.

Alternative biodegradable acrylates are mentioned. Drugs can be incorporated into nanoparticles by either direct incorporation during the polymerization process or adsorption to preformed nanoparticles. The efficiency of the incorporation and the release characteristics of model compounds as well as anticancer drugs are discussed. Methods for examining these processes, including the determination of adsorption and desorption, kinetics, and isotherms, are mentioned. Selectivity in drug targeting can, in theory, be achieved by the attachment of some form of homing device, normally a monoclonal antibody or a lectin. Work in vitro and in vivo, where nanoparticles have been coated with monoclonal antibodies, is described. Finally, methods for the labeling of nanoparticles with gamma-emitting radionuclides are presented, and results obtained in animal species are given.

L22 ANSWER 4 OF 29 USPATFULL

96:108621 Method of preparing a stable colloid of submicron particles.

Ziolo, Ronald F., Webster, NY, United States

Xerox Corporation, Stamford, CT, United States (U.S. corporation)

US 5578245 961126

APPLICATION: US 94-303644 940909 (8)

DOCUMENT TYPE: Utility.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides submicron particles. The invention further provides submicron particles which are dispersed in an aqueous colloid. The invention further provides a method of forming the stable dispersion which includes providing an ion exchange resin, loading the ion exchange resin with an ion, treating the loaded resin to form \*\*\*nanoscale\*\*\* particles. The invention further provides fluidizing the resin and particles to form an aqueous stable colloid.

L33 ANSWER 1 OF 6 MEDLINE

95193247 In vitro assembly of \*\*\*cowpea\*\*\* \*\*\*chlorotic\*\*\*  
 \*\*\*mottle\*\*\* \*\*\*virus\*\*\* from \*\*\*coat\*\*\* \*\*\*protein\*\*\*  
 expressed in Escherichia coli and in vitro-transcribed viral cDNA.  
 Zhao X; Fox J M; Olson N H; Baker T S; Young M J. (Department of  
 Biological Sciences, Purdue University, West Lafayette, Indiana  
 47907. )VIROLOGY, (1995 Mar 10) 207 (2) 486-94. Journal code: XEA.  
 ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The small spherical plant virus, \*\*\*cowpea\*\*\* \*\*\*chlorotic\*\*\*  
 \*\*\*mottle\*\*\* \*\*\*virus\*\*\* ( \*\*\*CCMV\*\*\* ), provides an ideal  
 system to examine spherical virus assembly. We have modified the  
 \*\*\*CCMV\*\*\* in vitro assembly system to produce virions from  
 \*\*\*coat\*\*\* \*\*\*protein\*\*\* expressed in Escherichia coli and  
 viral RNA transcribed in vitro from full-length cDNAs. Examination  
 of the in vitro-assembled \*\*\*particles\*\*\* with cryoelectron  
 microscopy and image reconstruction techniques demonstrates that the  
 \*\*\*particles\*\*\* are indistinguishable from plant purified  
 \*\*\*particles\*\*\* at 2.5 nm resolution. Mutational analysis of the  
 \*\*\*coat\*\*\* \*\*\*protein\*\*\* N- and C-terminal extensions  
 demonstrate their respective roles in virus assembly. The N-terminus  
 is required for assembly of RNA containing \*\*\*particles\*\*\* but  
 not for the assembly of empty virions. The C-terminus is essential  
 for \*\*\*coat\*\*\* \*\*\*protein\*\*\* dimer formation and  
 \*\*\*particle\*\*\* assembly.

L3 ANSWER 5 OF 13 MEDLINE

96400116 Document Number: 96400116. Analysis of a salt stable mutant of  
 cowpea chlorotic mottle \*\*\*virus\*\*\* . Fox J M; Zhao X; Speir J A;  
 \*\*\*Young M J\*\*\* . (Department of Biological Sciences, Purdue University,  
 West Lafayette, Indiana 47907, USA. )VIROLOGY, (1996 Aug 1) 222 (1)  
 115-22. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States.  
 Language: English.

AB An understanding of \*\*\*virion\*\*\* assembly and disassembly requires a  
 detailed understanding of the protein-protein and protein-nucleic acid  
 interactions which stabilize the \*\*\*virion\*\*\* . We have characterized a  
 mutant of cowpea chlorotic mottle \*\*\*virus\*\*\* (CCMV) that is altered  
 in \*\*\*virion\*\*\* stability. The mutant \*\*\*virions\*\*\* resist  
 disassembly in 1.0 M NaCl, pH 7.5, whereas the wild-type \*\*\*virions\*\*\*  
 completely disassociate into RNA and capsid protein components. Sequence  
 analysis of the mutant coat protein gene identified a single A to G  
 nucleotide change at position 1484 of RNA 3 (position 134 of RNA 4), which  
 results in a lysine to arginine change at position 42 of the coat protein.  
 Introduction of the K42R mutation into wild-type CCMV coat protein results  
 in a salt stable \*\*\*virion\*\*\* phenotype. Likewise, expression of the  
 K42R mutant coat protein in Escherichia coli followed by in vitro assembly  
 produces \*\*\*virions\*\*\* that exhibit the salt stable phenotype.  
 Analysis of this mutation demonstrates how a single amino acid change in  
 the primary structure of the coat protein leads to tertiary interactions  
 which stabilize the \*\*\*virion\*\*\* .

L3 ANSWER 2 OF 13 MEDLINE

97296233 Document Number: 97296233. \*\*\*Virion\*\*\* swelling is not  
 required for cotranslational disassembly of cowpea chlorotic mottle  
 \*\*\*virus\*\*\* in vitro. Albert F G; Fox J M; \*\*\*Young M J\*\*\* .  
 (Department of Plant Pathology, Montana State University, Bozeman 59717,  
 USA. )JOURNAL OF VIROLOGY, (1997 Jun) 71 (6) 4296-9. Journal code: KCV.  
 ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The mechanism by which \*\*\*virions\*\*\* of cowpea chlorotic mottle  
 \*\*\*virus\*\*\* (CCMV) disassemble and allow for translation of the  
 \*\*\*virion\*\*\* RNA is not well understood. Previous models have suggested  
 that \*\*\*virion\*\*\* swelling is required to expose the \*\*\*virion\*\*\*  
 RNA for translation in a process referred to as cotranslational  
 disassembly (M. Brisco, R. Hull, and T. M. A. Wilson, \*\*\*Virology\*\*\*  
 148:210-217, 1986; J. W. Roenhorst, J. W. M. van Lent, and B. J. M.  
 Verduin, \*\*\*Virology\*\*\* 164:91-98, 1988; J. W. Roenhorst, J. M.  
 Verduin, and R. W. Goldbach, \*\*\*Virology\*\*\* 168:138-146, 1989).  
 Previous work in our laboratory has identified point mutations in the CCMV

coat protein which result in \*\*\*virions\*\*\* with altered swelling characteristics (J. Fox, F. G. Albert, J. Speir, and M. J. Young, \*\*\*Virology\*\*\* 227:229-233, 1997; J. M. Fox, X. Zhao, J. A. Speir, and M. J. Young, \*\*\*Virology\*\*\* 222:115-122, 1996). The wild-type and mutant CCMV \*\*\*virions\*\*\* were used to correlate \*\*\*virion\*\*\* swelling with the ability of \*\*\*virion\*\*\* RNA to be translated in a cell-free wheat germ extract. Mutant \*\*\*virions\*\*\* unable to swell (cpK42R) are as infectious as wild-type \*\*\*virions\*\*\* in vivo, and the levels of translated encapsidated \*\*\*virion\*\*\* RNA are similar to those of wild-type \*\*\*virions\*\*\* in vitro. Mutant \*\*\*virions\*\*\* capable of swelling but not of disassembling in vitro (cpR26C) are noninfectious and have severely reduced levels of translation of the encapsidated \*\*\*virion\*\*\* RNA in vitro. These studies suggest that \*\*\*virion\*\*\* swelling is not required for the cotranslational disassembly of CCMV. Additionally, the results indicate that there is a pH-dependent structural transition in the \*\*\*virion\*\*\*, other than swelling, that results in the RNA's being exposed for translation in vitro. An alternative model suggesting that cotranslational disassembly of CCMV involves presentation of the \*\*\*virion\*\*\* RNA through the \*\*\*virion\*\*\* fivefold axis is proposed.

L3 ANSWER 3 OF 13 MEDLINE

97167537 Document Number: 97167537. Characterization of a disassembly deficient mutant of cowpea chlorotic mottle \*\*\*virus\*\*\*. Fox J M; Albert F G; Speir J A; \*\*\*Young M J\*\*\*. (Department of Biological Sciences, Purdue University, West Lafayette, Indiana, 47907, USA. )VIROLOGY, (1997 Jan 6) 227 (1) 229-33. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB An understanding of \*\*\*virus\*\*\* disassembly requires a detailed understanding of the protein-protein and protein-nucleic acid interactions which stabilize the \*\*\*virion\*\*\*. We have characterized a mutant of cowpea chlorotic mottle \*\*\*virus\*\*\* [cpR26C (coat protein R26C)] that displays increased \*\*\*virion\*\*\* stability and is abnormal in \*\*\*virion\*\*\* disassembly when purified under nonreducing conditions. Reduced \*\*\*virions\*\*\* are infectious, whereas nonreduced \*\*\*virions\*\*\* are noninfectious. The cpR26C mutant \*\*\*virions\*\*\* purified under nonreducing conditions resist disassembly in 0.5 M CaCl<sub>2</sub>, pH 7.5. The nonreduced cpR26C mutant \*\*\*virions\*\*\* swell in neutral pH conditions (pH 7.5) but do not disassociate when the ionic strength is increased. In contrast, wild-type \*\*\*virions\*\*\* or cpR26C mutant \*\*\*virions\*\*\* isolated under reducing conditions completely disassociate into the RNA and capsid protein components at pH 7.5 and high ionic strength (i > 1.0). Sequence analysis of the cpR26C mutant identified a single C to U nucleotide change at position 1435 of RNA 3 (position 86 of RNA 4), which results in a arginine to cysteine change at position 26 of the coat protein. The cpR26C mutant provides an ideal chemical switch for examining \*\*\*virion\*\*\* assembly and disassembly.

L3 ANSWER 4 OF 13 MEDLINE

97138359 Document Number: 97138359. In vitro interactions of the aphid endosymbiotic SymL chaperonin with barley yellow dwarf \*\*\*virus\*\*\*. Filichkin S A; Brumfield S; Filichkin T P; \*\*\*Young M J\*\*\*. (Department of Plant Pathology, Montana State University, Bozeman 59717, USA. )JOURNAL OF VIROLOGY, (1997 Jan) 71 (1) 569-77. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Barley yellow dwarf \*\*\*virus\*\*\* (BYDV)-vector relationships suggest that there are specific interactions between BYDV \*\*\*virions\*\*\* and the aphid's cellular components. However, little is known about vector factors that mediate \*\*\*virion\*\*\* recognition, cellular trafficking, and accumulation within the aphid. Symbionins are molecular chaperonins produced by intracellular endosymbiotic bacteria and are the most abundant proteins found in aphids. To elucidate the potential role of symbionins in BYDV transmission, we have isolated and characterized two new symbionin symL genes encoded by the endosymbionts which are harbored by the BYDV aphid vectors Rhopalosiphum padi and Sitobion avenae. Endosymbiont symL-encoded proteins have extensive homology with the pea aphid SymL and Escherichia coli GroEL chaperonin. Recombinant and native SymL proteins can be assembled into oligomeric complexes which are similar to the GroEL

oligomer. R. padi SymL protein demonstrates an in vitro binding affinity for BYDV and its recombinant readthrough polypeptide. In contrast to the R. padi SymL, the closely related GroEL does not exhibit a significant binding affinity either for BYDV or for its recombinant readthrough polypeptide. Comparative sequence analysis between SymL and GroEL was used to identify potential SymL-BYDV binding sites. Affinity binding of SymL to BYDV in vitro suggests a potential involvement of endosymbiotic chaperonins in interactions with \*\*\*virions\*\*\* during their trafficking through the aphid.

L3 ANSWER 1 OF 13 MEDLINE

1998240948 Document Number: 98240948. Comparison of the native CCMV \*\*\*virion\*\*\* with in vitro assembled CCMV \*\*\*virions\*\*\* by cryoelectron microscopy and image reconstruction. Fox J M; Wang G; Speir J A; Olson N H; Johnson J E; Baker T S; \*\*\*Young M J\*\*\*. (Department of Plant Pathology, Montana State University-Bozeman, 59717, USA. )VIROLOGY, (1998 Apr 25) 244 (1) 212-8. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Cryoelectron microscopy and three-dimensional image reconstruction analysis has been used to determine the structure of native and in vitro assembled cowpea chlorotic mottle \*\*\*virus\*\*\* (CCMV) \*\*\*virions\*\*\* and capsids to 25-A resolution. Purified CCMV coat protein was used in conjunction with in vitro transcribed \*\*\*viral\*\*\* RNAs to assemble RNA 1 only, RNA 2 only, RNA 3/4 only, and empty (RNA lacking) \*\*\*virions\*\*\*. The image reconstructions demonstrate that the in vitro assembled CCMV \*\*\*virions\*\*\* are morphologically indistinguishable from native \*\*\*virions\*\*\* purified from infected plants. The \*\*\*viral\*\*\* RNA (vRNA) is packaged similarly within the different types of \*\*\*virions\*\*\*. The centers of all assembled particles are generally devoid of density and the vRNA packs against the interior surface of the \*\*\*virion\*\*\* shell. The vRNA appears to adopt an ordered conformation at each of the quasi-threefold axes.

L9 ANSWER 2 OF 4 MEDLINE

97456571 Document Number: 97456571. Studies of coat protein-mediated resistance to tobacco mosaic tobamovirus: correlation between \*\*\*assembly\*\*\* of mutant coat proteins and resistance. Bendahmane M; Fitchen J H; Zhang G; Beachy R N. (Department of Cell Biology, The Scripps Research Institute, La Jolla, California 92037, USA. )JOURNAL OF VIROLOGY, (1997 Oct) 71 (10) 7942-50. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Coat protein-mediated resistance (CP-MR) has been widely used to protect transgenic plants against virus diseases. To characterize the mechanisms of CP-MR to tobacco mosaic tobamovirus ( \*\*\*TMV\*\*\* ) we developed mutants of the coat protein that affected subunit-subunit interactions. Mutant CPs were expressed during \*\*\*TMV\*\*\* replication as well as in transgenic Nicotiana tabacum plants. The mutation T42-->W increased protein aggregation and T28-->W abolished aggregation and \*\*\*assembly\*\*\*, while the mutations T28-->W plus T42-->W and T89-->W altered normal CP subunit-subunit interactions. The mutant T28W was unable to assemble virus-like particles (VLPs) during infection and in transgenic plants failed to aggregate; this protein conferred no protection against challenge of transgenic plants by \*\*\*TMV\*\*\*. The mutant T42W had strong CP subunit-subunit interactions and formed VLPs but not infectious \*\*\*virions\*\*\*. Transgenic lines with this protein exhibited stronger protection against \*\*\*TMV\*\*\* infection than transgenic plants that contained the wild-type (wt) CP. It is proposed that increased resistance conferred by the T42W mutant results from strong interaction between transgenic CP subunits and challenge virus CP subunits. CP carrying the mutation T89-->W formed flexuous and unstable VLPs whereas the double mutant T28W:T42W formed open helical structures that accumulated as paracrystalline arrays. In transgenic plants, T89W and the double mutant CPs showed reduced ability to aggregate and provided lower protection against \*\*\*TMV\*\*\* infection than wt CP. A strong correlation between normal CP subunit-subunit interactions and CP-MR is observed, and a model for CP-MR involving interactions between the transgenic CP and the CP of the challenge virus as well as interference with virus movement is discussed.

L9 ANSWER 3 OF 4 MEDLINE

84158584 Document Number: 84158584. Coordinated two-disk nucleation, growth and properties, of virus-like particles assembled from \*\*\*tobacco\*\*\* - \*\*\*mosaic\*\*\* - \*\*\*virus\*\*\* capsid protein with poly(A) or oligo(A) of different length. Schon A; Mundry K W. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1984 Apr 2) 140 (1) 119-27. Journal code: EMZ. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB \*\*\*Assembly\*\*\* of nucleoprotein rods from \*\*\*tobacco\*\*\* \*\*\*mosaic\*\*\* \*\*\*virus\*\*\* ( \*\*\*TMV\*\*\* ) coat protein and poly(A) depends on the presence of 20S disks in a manner very similar to nucleation and growth of \*\*\*virions\*\*\* in reconstitution with \*\*\*TMV\*\*\* RNA. Products assembled with (A) approximately equal to 5000 appear to have the same buoyant density in CsCl, the same nucleotide/protein ratio and the same nuclease stability, as reconstituted and native \*\*\*TMV\*\*\*. Their rate of formation is very similar to the rate of reconstitution with \*\*\*TMV\*\*\* RNA when high-molecular-mass (A) approximately equal to 5000 is used, but becomes a function of chain length particularly with (A) less than or equal to 185. The composition of \*\*\*assembly\*\*\* products can be described sufficiently with the relation between number of capsid polypeptide monomers/particle, np, to the number of nucleotide residues/chain, nnt, of  $np = 1/3 (nnt + 50)$  with two important restrictions: (1) particles of less than four turns of helically arranged capsid subunits are unstable, and (2) particles with about 150 or less nucleotides per chain deviate in structure from mature virus and virus-like (= longer) \*\*\*assembly\*\*\* products. This is indicated by changes in both buoyant density in CsCl and optical properties, while 'dislocation' of the disk to the helical arrangement of capsid subunits ('helicalization') and nuclease stability already become established with chains as short as (A) approximately equal to 58 +/- 20. Consequently, we suggest that \*\*\*assembly\*\*\* proceeds through three distinct phases: (1) nucleation (resulting in helicalization) by interaction of nucleic acid with the first disk; (2) stabilization of the primary (unstable!) nucleation complex by addition of a second disk and formation of a four-turn virus-like and stable nucleoprotein helix, which is then fit for (3) elongation by addition of further disks. The question of what makes the \*\*\*TMV\*\*\* protein disk select specifically \*\*\*TMV\*\*\* RNA during virion \*\*\*assembly\*\*\* is discussed in some detail.

L13 ANSWER 6 OF 29 MEDLINE

96237421 Document Number: 96237421. A 'mixed' \*\*\*self\*\*\* - \*\*\*assembled\*\*\* monolayer for an impedimetric immunosensor. Rickert J; Gopel W; Beck W; Jung G; Heiduschka P. (Institute of Physical and Theoretical Chemistry, University of Tübingen, Germany. ) BIOSENSORS AND BIOELECTRONICS, (1996) 11 (8) 757-68. Journal code: AKA. ISSN: 0956-5663. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A synthetic peptide with the amino acid sequence 135-154 of the capsid protein VP1 of the foot-and-mouth-disease \*\*\*virus\*\*\* was modified with omega-hydroxyundecanethiol and applied together with non-derivatised omega-hydroxyundecanethiol for consecutive adsorption onto gold electrodes according to \*\*\*self\*\*\* - \*\*\*assembling\*\*\* procedures. The binding of a specific antibody to prepared recognition layers could be monitored by measurement of impedance or capacitance. In order to avoid non-specific effects, all measurements were performed in the presence of BSA. The complex between the antigenic peptide and the antibody was split by applying 6 M urea solution. The gold electrodes were mounted into an optimised flow-through system in order to perform capacitance-time measurements. The immobilised peptide can be recognised repeatedly by specific antibodies.

L13 ANSWER 8 OF 29 MEDLINE

95073964 Document Number: 95073964. \*\*\*Self\*\*\* - \*\*\*assembling\*\*\* process of cylindrical \*\*\*virus\*\*\* \*\*\*coat\*\*\* proteins as observed by synchrotron small-angle X-ray scattering. Sano Y; Inoue H; Kajiwara K; Urakawa H; Hiragi Y. (National Food Research Institute, Ibaraki. ) JOURNAL OF BIOCHEMISTRY, (1994 Jun) 115 (6) 1058-63. Journal code: HIF. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB The \*\*\*self\*\*\* - \*\*\*assembly\*\*\* process of cucumber green mottle

mosaic \*\*\*virus\*\*\* (CGMMV) protein and tobacco mosaic \*\*\*virus\*\*\* (TMV) protein was examined by the thermodynamic analysis of small-angle X-ray scattering (SAXS) data. Each polymerization step of the \*\*\*coat\*\*\* proteins was assumed to be specified by a single equilibrium constant, and the equilibrium constant was evaluated by fitting the size and shape of the constituents observed by SAXS to those calculated from an assumed polymerization scheme. The logarithmic plots of the equilibrium constant against the inverse of temperature were fitted with a straight line at each buffer concentration and the thermodynamic quantities were evaluated from its intercept (yielding entropy) and slope (yielding enthalpy). The enthalpy and entropy values of TMV protein were found to be independent of buffer concentration, whereas those of CGMMV protein depended strongly on buffer concentration. In the limit, as ionic strength tends to infinity, both the enthalpy and entropy values of CGMMV protein approach those of TMV protein. The higher negative surface charge of CGMMV protein is considered to be responsible for the formation of stable single-layered disks, and for the slow polymerization process even at higher temperature and higher buffer concentrations.

L13 ANSWER 10 OF 29 MEDLINE

94377493 Document Number: 94377493. Expression of tobacco mosaic \*\*\*virus\*\*\* \*\*\*coat\*\*\* protein and assembly of pseudovirus particles in Escherichia coli. Hwang D J; Roberts I M; Wilson T M. (AgBiotech Center, Cook College, Rutgers University, New Brunswick, NJ 08903. )PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Sep 13) 91 (19) 9067-71. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The bidirectional \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of tobacco mosaic \*\*\*virus\*\*\* (TMV, common or U1 strain) has been studied extensively in vitro. Foreign single-stranded RNA molecules containing the TMV origin-of-assembly sequence (OAS, 75-432 nt in length) are also packaged by TMV \*\*\*coat\*\*\* protein (CP) in vitro to form helical pseudovirus particles. To study \*\*\*virus\*\*\* assembly in vivo requires an easily manipulated model system, independent of replication in plants. The TMV assembly machinery also provides a convenient means to protect and recover chimeric gene transcripts of almost any length or sequence for a variety of applications. Native TMV CP expressed in and purified from Escherichia coli formed nonhelical, stacked aggregates after dialysis into pH 5 buffer and was inactive for in vitro assembly with TMV RNA. U1 CP derivatives in which the second amino acid was changed from Ser to Ala or Pro, nonacetylated N termini found in two natural strains of the \*\*\*virus\*\*\*, failed to remediate these anomalous properties. However, in vivo coexpression of CP and single-stranded RNAs (up to approximately 2 kb) containing the TMV OAS gave high yields of helical pseudovirus particles of the predicted length (up to 7.4 +/- 1.4 micrograms/mg of total bacterial protein). If the OAS-containing RNA was first recruited into bacterial polyribosomes, elongation of pseudovirus assembly was blocked. In vivo, E. coli expression of a full-length cDNA clone of the TMV genome (6.4 kb) resulted in high, immunodetectable levels of CP and assembly of sufficient intact genomic RNA to initiate systemic infection of susceptible tobacco plants.

L13 ANSWER 11 OF 29 MEDLINE

94328327 Document Number: 94328327. To build a \*\*\*virus\*\*\* capsid. An equilibrium model of the \*\*\*self\*\*\* \*\*\*assembly\*\*\* of polyhedral protein complexes. Zlotnick A. (Department of Biological Sciences, Purdue University, West Lafayette, IN 47907. )JOURNAL OF MOLECULAR BIOLOGY, (1994 Aug 5) 241 (1) 59-67. Journal code: J6V. ISSN: 0022-2836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The capsids of spherical (icosahedral) viruses are constructed of multiples of 60 subunits. The question of how these polymers assemble is basic to understanding the \*\*\*viral\*\*\* life cycle. A formalism describing \*\*\*virus\*\*\* assembly as an equilibrium between \*\*\*coat\*\*\* protein subunits, assembly intermediates and intact \*\*\*virus\*\*\* is presented. This equilibrium model of \*\*\*virus\*\*\* assembly is consistent with experimental observations of \*\*\*virus\*\*\* assembly. At equilibrium, either intact \*\*\*virus\*\*\* or free subunits are dominant species, assembly intermediates are predicted to be found only in trace

concentrations. The concentration of assembled \*\*\*virus\*\*\* at equilibrium is expected to be extremely concentration-dependent and resemble a highly cooperative reaction although the model does not explicitly include cooperativity. For statistical assembly of a polyhedron, a nucleus is not necessarily required and polymerization can proceed through a cascade of bimolecular reactions rather than a single higher order reaction. Thus, kinetics of assembly do not necessarily show the extreme concentration dependence typical of nucleated protein polymerization. Modest intersubunit interaction energies result in a very stable capsid; consequently, a small change in this interaction energy can result in a considerable change in the capsid-subunit equilibrium. Some possible effects of nucleation and protein-nucleic acid interactions on \*\*\*virus\*\*\* assembly and capsid morphology are considered.

L13 ANSWER 12 OF 29 MEDLINE

94305433 Document Number: 94305433. Assembly of tobacco mosaic \*\*\*virus\*\*\* and TMV-like pseudovirus particles in Escherichia coli. Hwang D J; Roberts I M; Wilson T M. (AgBiotech Center, Cook College, Rutgers University, New Brunswick, New Jersey. )ARCHIVES OF VIROLOGY. SUPPLEMENTUM, (1994) 9 543-58. Journal code: BLI. ISSN: 0939-1983. Pub. country: Austria. Language: English.

AB High-level expression of plant \*\*\*viral\*\*\* proteins, including \*\*\*coat\*\*\* protein (CP), is possible in Escherichia coli. Native tobacco mosaic \*\*\*virus\*\*\* (TMV) CP expressed in E. coli remains soluble but has a non-acetylated N-terminal Ser residue and following extraction, is unable to package TMV RNA in vitro under standard assembly conditions. Changing the Ser to Ala or Pro by PCR-mutagenesis did not confer assembly competence in vitro, despite these being non-acetylated N-termini present in two natural strains of TMV. All TMV CPs made in E. coli formed stacked cylindrical aggregates in vitro at pH 5.0 and failed to be immunogold-labelled using a mouse monoclonal antibody specific for helically assembled TMV CP. TMV \*\*\*self\*\*\* - \*\*\*assembly\*\*\* has been studied extensively in vitro, and an origin of assembly sequence (OAS) mapped internally on the 6.4 kb ssRNA genome. Pseudovirus particles can be assembled mono- or bi-directionally in vitro using \*\*\*virus\*\*\*-derived CP and chimeric ssRNAs containing the cognate TMV OAS, but otherwise of unlimited length and sequence. Studies on plant \*\*\*virus\*\*\* assembly in vivo would be facilitated by a model system amenable to site-directed mutagenesis and rapid recovery of progeny particles. When chimeric transcripts containing the TMV OAS were co-expressed with TMV CP in vivo for 2-18 h, helical TMV-like ribonucleoprotein particles of the predicted length were formed in high yield (up to 7.4 micrograms/mg total bacterial protein). In addition to providing a rapid, inexpensive and convenient system to produce, protect and recover chimeric gene transcripts of any length or sequence, this E. coli system also offers a rapid approach for studying the molecular requirements for plant \*\*\*virus\*\*\* " \*\*\*self\*\*\* - \*\*\*assembly\*\*\* " in vivo. Transcription of a full-length cDNA clone of TMV RNA also resulted in high levels of CP expression and assembly of sufficient intact genomic RNA to initiate \*\*\*virus\*\*\* infection of susceptible tobacco plants.

L13 ANSWER 17 OF 29 MEDLINE

91188946 Document Number: 91188946. Switching in the \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of tobacco mosaic \*\*\*virus\*\*\*. Caspar D L; Namba K. (Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, Massachusetts 02254.. )ADVANCES IN BIOPHYSICS, (1990) 26 157-85. Ref: 63. Journal code: 2J2. ISSN: 0065-227X. Pub. country: Ireland. Language: English.

AB Experimental observations on the structure and physicochemical properties of TMV protein assemblies have led to a fundamental switch in the model of the \*\*\*self\*\*\* - \*\*\*assembly\*\*\* process: rather than being nucleated by the hypothetical two-layer disk, \*\*\*virus\*\*\* assembly appears to be initiated by interaction of the specific RNA sequence with a short helical aggregate of the \*\*\*coat\*\*\* protein arranged as in the \*\*\*virus\*\*\*. Formation of the 20s nucleating aggregate involves the binding of an average of half a proton per protein subunit. This proton-binding site can be identified with the carboxyl-carboxylate pair that is formed between top and bottom protein surfaces at a radius of 58 A in the \*\*\*virus\*\*\*



helix. Because the 20S aggregate consists of about two helical turns, only one carboxyl-carboxylate pair will be formed between each top-bottom pair of protein subunits. Limitation of the length of the 20S helical aggregate at neutral pH can be accounted for by disorder of the inner loop of the protein chain, due to electrostatic repulsion among the carboxyl groups that form the anomalous proton-binding site at 25 Å radius in the ordered \*\*\*virus\*\*\* structure. To grow beyond two to three turns, inner loops of the protein at the interior of the helix must be ordered in the close-packed arrangement. The electrostatic repulsion opposing this ordering can be overcome by binding of the \*\*\*viral\*\*\* RNA at neutral pH, by calcium binding, or by proton binding in slightly acid solution. \*\*\*Virus\*\*\* disassembly upon infection appears to result from the low intracellular calcium and proton concentration compared to the extracellular environment, which increases the electrostatic repulsion among the negatively charged groups involved in calcium and proton binding, thereby allowing cellular ribosomes to competitively bind the \*\*\*viral\*\*\* RNA. Disk aggregates of TMV protein, which form at high ionic strength in alkaline solution, do not appear to be involved in \*\*\*virus\*\*\* assembly. The stacked-disc aggregate, which was previously presumed to be built of a polar stack of the hypothetical polar two-layer aggregate, is, in fact, a bipolar structure. Because the bonding between turns of the disc structures is different from that of the \*\*\*virus\*\*\* helix, direct switching between these structures by the postulated dislocation does not occur. TMV assembly does appear to involve conservation of bonding specificity, as initially presumed, but only in helical packing arrangements of the protein subunits. Switching from disordered to ordered conformations of the protein, dependent on changes in the electrostatic interactions among the protein subunits, appears to be critical in controlling the assembly process.

L13 ANSWER 19 OF 29 MEDLINE

90335207 Document Number: 90335207. Preparation and properties of recombinant DNA derived tobacco mosaic \*\*\*virus\*\*\* \*\*\*coat\*\*\* protein. Shire S J; McKay P; Leung D W; Cachianes G J; Jackson E; Wood W I; Raghavendra K; Khairallah L; Schuster T M. (Department of Pharmaceutical Research and Development, Genetech, Inc., South San Francisco, California 94080.. ) BIOCHEMISTRY, (1990 May 29) 29 (21) 5119-26. Journal code: A0G. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Recombinant DNA derived tobacco mosaic \*\*\*virus\*\*\* (vulgare strain) \*\*\*coat\*\*\* protein (r-TMVP) was obtained by cloning and expression in *Escherichia coli* and was purified by column chromatography, \*\*\*self\*\*\* - \*\*\*assembly\*\*\* polymerization, and precipitation. SDS-PAGE, amino terminal sequencing, and immunoblotting with polyclonal antibodies raised against TMVP confirmed the identify and purity of the recombinant protein. Isoelectric focusing in 8 M urea and fast atom bombardment mass spectrometry demonstrated that the r-TMVP is not acetylated at the amino terminus, unlike the wild-type protein isolated from the tobacco plant derived \*\*\*virus\*\*\*. The characterization of r-TMVP with regard to its \*\*\*self\*\*\* - \*\*\*assembly\*\*\* properties revealed reversible endothermic polymerization as studied by analytical ultracentrifugation, circular dichroism, and electron microscopy. However, the details of the assembly process differed from those of the wild-type protein. At neutral pH, low ionic strength, and 20 degrees C, TMVP forms a 20S two-turn helical rod that acts as a nucleus for further assembly with RNA and additional TMVP to form TMV. Under more acidic conditions, this 20S structure also acts as a nucleus for protein \*\*\*self\*\*\* - \*\*\*assembly\*\*\* to form viruslike RNA-free rods. The r-TMVP that is not acetylated carries an extra positive charge at the amino terminus and does not appear to form the 20S nucleus. Instead, it forms a 28S four-layer structure, which resembles in size and structure the dimer of the bilayer disk formed by the wild-type protein at pH 8.0, high ionic strength, and 20 degrees C. (ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 28 OF 29 MEDLINE

81101234 Document Number: 81101234. Structural studies of the assembly of simple viruses. Makowski L. PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, (1980) 40 233-58. Ref: 135. Journal code: PZ5. ISSN: 0361-7742. Pub.

country: United States. Language: English.

AB The principles of structural design and the bonding properties of structural proteins form a basis for the study of \*\*\*virus\*\*\* assembly. \*\*\*Virus\*\*\* \*\*\*coat\*\*\* proteins are designed specifically to interact with one another and with the \*\*\*viral\*\*\* nucleic acid to form a stable \*\*\*virus\*\*\* particle. The process of assembly is controlled by the switching of protein subunit conformation, which can alter the binding properties of the subunits. The \*\*\*self\*\*\* - \*\*\*assembly\*\*\* processes of several simple viruses in vitro have significantly different rates of assembly and specificities for their \*\*\*viral\*\*\* nucleic acid. It is possible that many viruses have multiple pathways for assembly, each pathway exhibiting somewhat different characteristics but all resulting in identical infectious \*\*\*virus\*\*\* particles.

L13 ANSWER 29 OF 29 MEDLINE

68241037 Document Number: 68241037. The \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of spherical viruses with mixed \*\*\*coat\*\*\* proteins. Wagner G W; Bancroft J B. VIROLOGY, (1968 Apr) 34 (4) 748-56. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

L14 ANSWER 168 OF 212 MEDLINE

83189126 Document Number: 83189126. \*\*\*Self\*\*\* - \*\*\*assembly\*\*\* of brome mosaic \*\*\*virus\*\*\* protein into capsids. Initial and final states of aggregation. Cuillel M; Zulauf M; Jacrot B. JOURNAL OF MOLECULAR BIOLOGY, (1983 Mar 15) 164 (4) 589-603. Journal code: J6V. ISSN: 0022-2836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The pH and ionic strength dependence of the states of aggregation of brome mosaic \*\*\*virus\*\*\* protein has been investigated by small angle neutron scattering, quasielastic light-scattering, analytical centrifugation and electron microscopy. At pH above neutrality, protein oligomers are found in dynamical equilibrium, comprising monomers, dimers and aggregates of higher molecular weight. By lowering the pH, capsids assemble spontaneously with dimensions in solution which depend on ionic strength. If formed by dialysis, they contain 180 monomers, but are 30 Å larger in diameter than the native \*\*\*virus\*\*\*. If formed by pH-jump, they contain less monomers: the deficiency decreases with decreasing the final pH and the initial protein concentration. Upon dehydration for electron microscopy, capsids contract by 10%.

L14 ANSWER 172 OF 212 MEDLINE

82242289 Document Number: 82242289. Poliovirus empty capsid morphogenesis: evidence for conformational differences between self- and extract-assembled empty capsids. Putnak J R; Phillips B A. JOURNAL OF VIROLOGY, (1982 Mar) 41 (3) 792-800. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In this paper we describe the use of specific proteinases, surface-specific radioiodination, and antigenic reactivity in conjunction with isoelectric focusing for probing the conformations of different polioviral empty capsid species. Naturally occurring empty capsids (called procapsids) with an isoelectric point of 6.8 were resistant to proteolytic digestion by trypsin or chymotrypsin, as were empty capsids assembled in vitro in the presence of a cytoplasmic extract prepared from poliovirus-infected HeLa cells. In contrast, \*\*\*self\*\*\* - \*\*\*assembled\*\*\* empty capsids (isoelectric point, 5.0) were sensitive to both proteinases. Capsid proteins VP0 and VP1 were attacked predominantly, whereas VP3 was resistant to cleavage. Unpolymerized 14S particles possessed a trypsin sensitivity which was qualitatively similar to that of \*\*\*self\*\*\* - \*\*\*assembled\*\*\* empty shells. Surface-specific iodination of virions and procapsids labeled VP1 exclusively. In contrast, radioiodination of \*\*\*self\*\*\* - \*\*\*assembled\*\*\* empty capsids labeled predominantly VP0. After radioiodination the sedimentation coefficient corrected to water at 20 degrees C, the isoelectric point, and the trypsin resistance of the procapsids remained unchanged. Procapsids and extract-assembled empty capsids were N antigenic, whereas \*\*\*self\*\*\* - \*\*\*assembled\*\*\* empty capsids were H antigenic. \*\*\*Self\*\*\* - \*\*\*assembled\*\*\* empty capsids were not converted to pH 6.8 trypsin-resistant structures by incubation with a \*\*\*virus\*\*\* -infected

cytoplasmic extract. However, 14S particles assembled in the presence of a mock-infected extract formed empty capsids, 20% of which resembled extract-assembled empty shells as determined by the above-described criteria. These and related findings are discussed in terms of empty capsid structure and morphogenesis.

L14 ANSWER 178 OF 212 MEDLINE

81233201 Document Number: 81233201. Studies on the mechanism of assembly of tobacco mosaic \*\*\*virus\*\*\*. Schuster T M; Scheele R B; Adams M L; Shire S J; Steckert J J; Potschka M. BIOPHYSICAL JOURNAL, (1980 Oct) 32 (1) 313-29. Journal code: A5S. ISSN: 0006-3495. Pub. country: United States. Language: English.

AB Sedimentation and proton binding studies on the endothermic self-association of tobacco mosaic \*\*\*virus\*\*\* (TMV) protein indicate that the so-called "20S" sedimenting protein is an interaction system involving at least the 34-subunit two-turn yield cylindrical disk aggregate and the 49-subunit three-turn helical rod. The pH dependence of this overall equilibrium suggests that disk formation is proton-linked through the binding of protons to the two-turn helix which is not present as significant concentrations near pH 7. There is a temperature-induced intramolecular conformation change in the protein leading to a difference spectrum which is complete in  $5 \times 10^{-6}$  s at pH 7 and 20 degrees C and is dominated at 300 nm by tryptophan residues. Kinetics measurements of protein polymerization, from  $10^{-6}$  to  $10^3$  s, reveal three relaxation processes at pH 7.0, 20 degrees C, 0.10 M ionic strength K (H) PO<sub>4</sub>. The fastest relaxation time is a few milliseconds and represents reactions within the 4S protein distribution. The second fastest relaxation is  $50-100 \times 10^{-3}$  s and represents elementary polymerization steps involved in the formation of the approximately 20 S protein. Analysis of the slowest relaxation, approximately  $5 \times 10^4$  s, suggests that this very slow formation of approximately 20 S protein may be dominated by some first order process in the overall dissociation of approximately 20S protein. Sedimentation measurements of the rate of TMV reconstitution, under the same conditions, show by direct measurements of 4S and approximately 20S incorporation at various 4S to approximately 20S weight ratios that the relative rate of approximately 20S incorporation decreases almost linearly, from 0 to 50% 4S. There appears to be one or more regions of TMV-RNA, approximately 1-1.5 kilobases long, which incorporates approximately 20S protein exclusively. Solutions of approximately 95-100% approximately 20S protein have been prepared for the first time and used for reconstitution with RNA. Such protein solutions yield full size TMV, but at a slower rate than if 4S protein is added. Thus the elongation reaction in TMV assembly, following nucleation with approximately 20S protein, is not exclusively dependent upon the presence of either 4S or approximately 20S protein aggregates. The initial, maximum, rate of reconstitution increases about threefold when the protein composition is changed from 5% to 30% 4S protein, at constant total protein concentration at pH 7.0, 20 degrees C in 0.10 M ionic strength K (H) PO<sub>4</sub>. The probable binding frame at the internal assembly nucleation site of TMV-RNA has been determined by measuring the association constants for the binding of various trinucleoside diphosphates to helical TMV protein rods. The -CAG-AAG-AAG-sequence at the nucleation site is capable of providing at least 10-14 kcal/mol of sites of binding free energy for the nucleation event in TMV \*\*\*self\*\*\* - \*\*\*assembly\*\*\*.

L14 ANSWER 179 OF 212 MEDLINE

81076640 Document Number: 81076640. Mechanism of RNA-protein interactions in tobacco mosaic \*\*\*virus\*\*\*: analysis of the pH stability of \*\*\*virus\*\*\* protein complexes with synthetic polynucleotides. Ledneva R K; Lanina T P; Terganova G V; Bogdanov A A. NUCLEIC ACIDS RESEARCH, (1980 Nov 11) 8 (21) 5129-41. Journal code: O8L. ISSN: 0301-5610. Pub. country: ENGLAND: United Kingdom. Language: English.

AB TMV-like RNP complexes were reconstituted from TMV protein and synthetic polynucleotides. Analysis of the pH stability of RNP with polynucleotides containing U, G, or their analogues reveals a correlation between the stability of their structure and the pK values of the bases, and indicates that the -NH-CO-groups of U and G are involved in hydrogen bonding with protein. It is suggested that TMV protein has two U- and one G-specific

binding sites which according to the phase position the protein subunits relative to the origin of TMV assembly (D. Zimmermann (1977), Cell 11, 463) are likely to be organized as UGU. The binding of the A and C residues of RNA with TMV protein is nonspecific. TMV protein groups with pK 6.3, 7.5 and 9.7 were found to be essential in the protein-protein interactions in RNP. A group of the protein with pK 8.2 is also involved in RNP stabilization. Both protein-protein interactions and interactions of protein with RNA phosphate groups were shown to be mediated by a conformational change in the protein induced by base binding. The effect of bases on both types of interactions changes in the order G approximately equal to much greater than A, and incorporation of C in RNP proceeds in a compulsory way at the expense of interaction of the neighbouring nucleotide residues in polynucleotides with protein. The data obtained are used to discuss the principles of the cooperativity of the interactions between TMV components and the mechanism of initiation and elongation in TMV \*\*\*self\*\*\* - \*\*\*assembly\*\*\* .

L14 ANSWER 193 OF 212 MEDLINE

76103156 Document Number: 76103156. \*\*\*Self\*\*\* - \*\*\*assembly\*\*\* of biological macromolecules. Perham R N. PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON. SERIES B: BIOLOGICAL SCIENCES, (1975 Nov 6) 272 (915) 123-36. Journal code: P5Z. ISSN: 0080-4622. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The genetic apparatus of the cell is responsible for the accurate biosynthesis of the primary structure of macromolecules which then spontaneously fold up and, in certain circumstances, aggregate to yield the complex tertiary and quaternary structures of the biologically active molecules. Structures capable of \*\*\*self\*\*\* - \*\*\*assembly\*\*\* in this range from simple monomers through oligomers to complex multimeric structures that may contain more than one type of polypeptide chain and components other than protein. It is becoming clear that even with the simpler monomeric enzymes there is becoming clear that even with the simpler monomeric enzymes there is a kinetically determined pathway for the folding process and that a folded protein must now be regarded as the minimum free energy form of the kinetically accessible conformations. It is argued that the denatured subunits of oligomeric enzymes are likely to fold to something like their final structure before aggregating to give the native quaternary structure and the available evidence would suggest that this is so. The importance of nucleation events and stable intermediates in the \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of more complex structures is clear. Many \*\*\*self\*\*\* - \*\*\*assembling\*\*\* structures contain only identical subunits and symmetry arguments are very successful in accounting for the structures formed. Because proteins are themselves complex molecules and not inelastic geometric objects, the rules of strict symmetry can be bent and quasi-equivalent bonding between subunits permitted. This possibility is frequently employed in biological structures. Conversely, symmetry arguments can offer a reliable means of choosing between alternative models for a given structure. It can be seen that proteins gain stability by growing larger and it is argued in evolutionary terms that aggregation of subunits is the preferred way to increase the size of proteins. The possession of quaternary structure by enzymes allows conferral of other biologically important properties, such as cooperativity between active sites, changes of specificity, substrate channelling and sequential reactions within a multi-enzyme complex. Comparison is made of the invariant subunit compositions of the simpler oligomeric enzymes with the variation evidently open to, say, the 2-oxoacid dehydrogenase complexes of E. coli. With viruses, on the other hand, the function of the quaternary structure is to package nucleic acid and, as an example, the assembly and breakdown of tobacco mosaic \*\*\*virus\*\*\* is discussed. Attention is drawn to the possible ways in which the principles of \*\*\*self\*\*\* - \*\*\*assembly\*\*\* can be extended to make structures more complicated than those that can be formed by simple aggregation of the component parts.

L14 ANSWER 199 OF 212 MEDLINE

71276880 Document Number: 71276880. In vitro assembly of poliovirus. II. Evidence for the \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of 14 S particles into empty capsids. Phillips B A. VIROLOGY, (1971 May) 44 (2) 307-16. Journal

code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

L14 ANSWER 201 OF 212 MEDLINE

71091872 Document Number: 71091872. The \*\*\*self\*\*\* - \*\*\*assembly\*\*\* of spherical plant viruses. Bancroft J B. ADVANCES IN VIRUS RESEARCH, (1970) 16 99-134. Ref: 81. Journal code: 2PW. ISSN: 0065-3527. Pub. country: United States. Language: English.

L14 ANSWER 212 OF 212 MEDLINE

67126651 Document Number: 67126651. A study of the \*\*\*self\*\*\* - \*\*\*assembly\*\*\* process in a small spherical \*\*\*virus\*\*\*. Formation of organized structures from protein subunits in vitro. Bancroft J B; Hills G J; Markham R. VIROLOGY, (1967 Feb) 31 (2) 354-79. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

L16 ANSWER 15 OF 17 MEDLINE

91354536 Document Number: 91354536. Use of liposomes, \*\*\*viral\*\*\* capsids, and \*\*\*nanoparticles\*\*\* as DNA carriers. Bertling W M; Gareis M; Paspaleeva V; Zimmer A; Kreuter J; Nurnberg E; Harrer P. (Clinical Research Units Rheumatology, Max-Planck Society, University of Erlangen-Nurnberg, Germany. ) BIOTECHNOLOGY AND APPLIED BIOCHEMISTRY, (1991 Jun) 13 (3) 390-405. Journal code: AHF. ISSN: 0885-4513. Pub. country: United States. Language: English.

AB We tested a variety of liposomes for parameters such as DNA binding capacity and DNase I protection of incorporated and attached DNA to elucidate their use as vehicles for DNA transfer into cells and animals. The results were compared to other potential DNA vehicles, empty \*\*\*viral\*\*\* capsids, and \*\*\*nanoparticles\*\*\*. Maximal binding capacity was achieved for positively charged \*\*\*nanoparticles\*\*\*, DNase I protection was observed for most preparations with neosome preparations being least efficient. The uptake of radiolabeled DNA by cells in culture was determined for cationic and nonionic surfactant vesicles, \*\*\*viral\*\*\* capsids, and \*\*\*nanoparticles\*\*\*. Cellular DNA uptake was best for dioleoyl-derived positively charged liposomes (N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride; DOTMA) and the DNA could be shown to be physiologically active. The recombination rate for DNA fragments transfected in polyoma capsids in live mice was higher than for liposome mediated transfection. Homologous recombination could be observed for both DOTMA and polyoma-mediated DNA transfer.

L16 ANSWER 14 OF 17 MEDLINE

92016696 Document Number: 92016696. \*\*\*Nanoparticles\*\*\* and liposomes: a state of the art. Speiser P P. (Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich.. ) METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, (1991 Jun) 13 (5) 337-42. Ref: 0. Journal code: LZN. ISSN: 0379-0355. Pub. country: Spain. Language: English.

AB The loading of drugs into ultrafine host vesicles or colloidal capsules in the nanometer size range is an acknowledged technique for the optimization of controlled drug delivery. The main purpose will always be to design inert auxiliary accompanying materials; to use body-friendly and biodegradable excipients; and to miniaturize the drug carrier system dramatically in order to get good stability, excellent absorption, quantitative tissular transfer and, therefore, the expected pharmacodynamic activity. Furthermore, side effects and foreign body irritation should be avoided and a good local and systemic tolerance during and after medication should be a condition sine qua non. The actual state of the art is shown with 4 practical application examples, namely: a cellular uptake by endocytosis and a specific lysosomotropic cell transfer with cell tracer-loaded \*\*\*nanoparticles\*\*\*; the strong immunosuppressive stimulation of nanocapsules--as new adjuvants--when loaded with \*\*\*viral\*\*\* or other antigens; the better blood-brain barrier transfer of an antiparkinson drug when covalently bound to special liposomes; and the use of minivesicles for controlled site-specific anticancer drug release (tumor targeting). In the future, we must find a possibility to deliver the correct dose of the drug precisely to the diseased target organs, tissues or cells of destination, without flooding

the organism with massive drug doses. One technological answer could be the minicarrier concept with specific pathfinders and aspecific pretargeters that serve as switchmen to guide the drug-loaded carrier to the organs, with precise spot landing.

L16 ANSWER 7 OF 17 MEDLINE

96338368 Document Number: 96338368. Efficiency of \*\*\*nanoparticles\*\*\* as a carrier system for antiviral agents in human immunodeficiency \*\*\*virus\*\*\* -infected human monocytes/macrophages in vitro. Bender A R; von Briesen H; Kreuter J; Duncan I B; Rubsamen-Waigmann H. (Chemotherapeutical Research Institute Georg-Speyer-Haus, Frankfurt am Main, Germany. )ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Jun) 40 (6) 1467-71. Journal code: 6HK. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Polyhexylcyanoacrylate \*\*\*nanoparticles\*\*\* loaded with either the human immunodeficiency \*\*\*virus\*\*\* (HIV) protease inhibitor saquinavir (Ro 31-8959) or the nucleoside analog zalcitabine (2',3'-dideoxycytidine) were prepared by emulsion polymerization and tested for antiviral activity in primary human monocytes/macrophages in vitro. Both nanoparticulate formulations led to a dose-dependent reduction of HIV type 1 antigen production. While \*\*\*nanoparticle\*\*\* -bound zalcitabine showed no superiority to an aqueous solution of the drug, a significantly higher efficacy was observed with saquinavir-loaded \*\*\*nanoparticles\*\*\*. In acutely infected cells, an aqueous solution of saquinavir showed little antiviral activity at concentrations below 10 nM, whereas the nanoparticulate formulation exhibited a good antiviral effect at a concentration of 1 nM and a still-significant antigen reduction at 0.1 nM (50% inhibitory concentrations = 4.23 nM for the free drug and 0.39 nM for the \*\*\*nanoparticle\*\*\* -bound drug). At a concentration of 100 nM, saquinavir was completely inactive in chronically HIV-infected macrophages, but when bound to \*\*\*nanoparticles\*\*\* it caused a 35% decrease in antigen production. Using \*\*\*nanoparticles\*\*\* as a drug carrier system could improve the delivery of antiviral agents to the mononuclear phagocyte system in vivo, overcoming pharmacokinetic problems and enhancing the activities of drugs for the treatment of HIV infection and AIDS.

L16 ANSWER 5 OF 17 MEDLINE

97158173 Document Number: 97158173. A new family of carriers (biovectors) enhances the immunogenicity of rabies antigens. Castignolles N; Morgeaux S; Gontier-Jallet C; Samain D; Betbeder D; Perrin P. (Laboratoire des Lyssavirus, Institut Pasteur, Paris, France. )VACCINE, (1996 Oct) 14 (14) 1353-60. Journal code: X6O. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Biovectors (BV) are a new family of protein carriers. They are \*\*\*nanoparticles\*\*\* of polymerized polysaccharides substituted with phosphate residues and surrounded by covalently bound lipid molecules (palmitic acid). The effect of BV was tested on the immunogenicity of rabies antigens. Biovectors enhanced the production of antibody induced by both rabies glycoprotein and ribonucleoprotein. Moreover, they enhanced the protective activity of an experimental rabies vaccine composed of inactivated and purified \*\*\*virus\*\*\*. The isotype profile of antibody produced in vivo was not modified when BV were mixed with rabies antigens. To clarify the mechanism of the adjuvant/ immunostimulation effect of BV, two types of approach were used: (1) analysis of the antibody response when antigen and BV were injected separately; (2) determination of the nature of cells involved in the proliferation in vitro of murine splenocytes in the presence of BV. The enhancing effect of BV on antibody production was highest when mixed with antigens. In vitro BV induced the proliferation of B cells. These findings suggest that BV have immunostimulating properties in addition to their probable depot and/or antigen-presentation effect which explain in part their adjuvant activity.

L16 ANSWER 2 OF 17 MEDLINE

1998297657 Document Number: 98297657. A physicochemical approach for predicting the effectiveness of peptide-based gene delivery systems for use in plasmid-based gene therapy. Duguid J G; Li C; Shi M; Logan M J; Alila H; Rolland A; Tomlinson E; Sparrow J T; Smith L C. (GeneMedicine,

- AB Novel synthetic peptides, based on carrier peptide analogs (YKAKnWK) and an amphipathic peptide (GLFEALLELLESLWELLLEA), have been formulated with DNA plasmids to create peptide-based gene delivery systems. The carrier peptides are used to condense plasmids into \*\*\*nanoparticles\*\*\* with a hydrodynamic diameter (DH) ranging from 40 to 200 nm, which are sterically stable for over 100 h. Size and morphology of the carrier peptide/plasmid complex have been determined by photon correlation spectroscopy (PCS) and transmission electron microscopy (TEM), respectively. The amphipathic peptide is used as a pH-sensitive lytic agent to facilitate release of the plasmid from endosomes after endocytosis of the peptide/plasmid complex. Hemolysis assays have shown that the amphipathic peptide destabilizes lipid bilayers at low pH, mimicking the properties of \*\*\*viral\*\*\* fusogenic peptides. However, circular dichroism studies show that unlike the \*\*\*viral\*\*\* fusion peptides, this amphipathic peptide loses some of its alpha-helical structure at low pH in the presence of liposomes. The peptide-based gene delivery systems were tested for transfection efficiency in a variety of cell lines, including 14-day C2C12 mouse myotubes, using gene expression systems containing the beta-galactosidase reporter gene. Transfection data demonstrate a correlation between in vitro transfection efficiency and the combination of several physical properties of the peptide/plasmid complexes, including 1) DNA dose, 2) the zeta potential of the particle, 3) the requirement of both lytic and carrier peptides, and 4) the number of lysine residues associated with the carrier peptide. Transfection data on 14-day C2C12 myotubes utilizing the therapeutic human growth hormone gene formulated in an optimal peptide gene delivery system show an increase in gene expression over time, with a maximum in protein levels at 96 h (approximately 18 ng/ml).

L23 ANSWER 3 OF 19 CAPLUS COPYRIGHT 1999 ACS

1998:322201 Document No. 129:78171 Host-guest encapsulation of materials by assembled virus protein cages. \*\*\*Douglas, Trevor\*\*\* ; Young, Mark (Dep. Chem., Temple Univ., Philadelphia, PA, 19122-2585, USA). Nature (London), 393(6681), 152-155 (English) 1998. CODEN: NATUAS. ISSN: 0028-0836. Publisher: Macmillan Magazines.

- AB Self-assembled cage structures of nanometer dimensions can be used as constrained environments for the prepn. of nanostructured materials and the encapsulation of guest mol.s., with potential applications in drug delivery and catalysis. In synthetic systems the no. of subunits contributing to cage structures is typically rather small. But the protein coat of viruses (virions) commonly comprise hundreds of subunits that self-assemble into a cage for transporting viral nucleic acids. Many virions, moreover, can undergo reversible structural changes that open or close gated pores to allow switchable access to their interior. Here the authors show that such a virion - that of the cowpea chlorotic mottle virus - can be used as a host for the synthesis of materials. The authors report the mineralization of two polyoxometalate species (paratungstate and decavanadate) and the encapsulation of an anionic polymer inside this virion, controlled by pH-dependent gating of the virion's pores. The diversity in size and shape of such virus particles make this a versatile strategy for materials synthesis and mol. entrapment.

L23 ANSWER 7 OF 19 CAPLUS COPYRIGHT 1999 ACS

1996:470209 Document No. 125:107917 Biomimetic synthesis of nanoscale particles in organized protein cages. \*\*\*Douglas, Trevor\*\*\* (Department biological and Physical Sciences, Montana State University, Billings, MT, 59101, USA). Biomimetic Mater. Chem., 91-115. Editor(s): Mann, Stephen. VCH: New York, N. Y. (English) 1996. CODEN: 63DGAS.

- AB A review, with 72 refs. The intrinsic properties of the unique supramol. protein assembly of ferritin facilitate the formation of stable nanoscale particles. These properties include a quaternary structure that defines a spatially constrained cavity, a biodegradable and biol. compatible polymer matrix.

L23 ANSWER 8 OF 19 CAPLUS COPYRIGHT 1999 ACS

1995:679042 Document No. 123:117278 Synthesis and structure of an iron(III)

sulfide-ferritin bioorganic nanocomposite. \*\*\*Dolan, Trevor\*\*\* ;  
Dickson, Dominic P. L.; Betteridge, Steven; Charnock, John; Garner, C.  
David; Mann, Stephen (Sch. Chem., Univ. Bath, Bath, BA2 7AY, UK). Science  
(Washington, D. C.), 269(5220), 54-7 (English) 1995. CODEN: SCIEAS.  
ISSN: 0036-8075.

AB Amorphous iron sulfide minerals contg. either 500 or 3000 iron atoms in  
each cluster have been synthesized in-situ within the nanodimensional  
cavity of horse spleen ferritin. Iron-57 Moessbauer spectroscopy  
indicated that most of the iron atoms in the 3000-iron atom cores are  
trivalent, whereas in the 500-iron atom clusters, .apprx.50% of the iron  
atoms are Fe(III), with the remaining atoms having an effective oxidn.  
state of .apprx.+2.5. Iron K-edge extended x-ray absorption fine  
structure data for the 500-iron atom nanocomposite were consistent with a  
disordered array of edge-shared FeS<sub>4</sub> tetrahedra, connected by FeS<sub>2</sub>-Fe  
bridges with bond lengths similar to those of the cubane-type motif of  
Fe-S clusters. The approach used here for the controlled synthesis of  
bioinorg. nanocomposites could be useful for the nanoscale engineering of  
dispersed materials with biocompatible and bioactive properties.